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Letter to the Editor

Time-resolved sex differences in language lateralization

S. Ortigue, G. Thut, T. Landis and C. M. Michel

Functional Brain Mapping Laboratory, Department of Neurology, University Hospital and Department of Fundamental Neuroscience, University Medical School, Geneva, Switzerland

Correspondence to: Christoph M. Michel, Functional Brain Mapping Laboratory, Neurology Clinic, University Hospital, 1211 Geneva, Switzerland
E-mail: christoph.michel@medecine.unige.ch
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Many clinical, behavioural and brain imaging studies have suggested that language functions are less asymmetrical in women than in men. Sommer and colleagues challenge this view in a recent review on the outcome of 24 functional brain imaging studies (PET, functional MRI or functional transcranial Doppler ultrasound) that looked at possible sex differences in language lateralization. A vote count analysis over all studies revealed a much higher score for those studies that reported no sex differences. In addition, a meta-analysis of the lateralization index in 13 of these studies revealed no statistically significant difference between men and women. The authors concluded that the hypothesis of sex differences in cortical language representation probably has to be rejected at the population level (Sommer *et al*., 2004). We believe that the hypothesis of subtle, but crucial sex differences in language representation should not be rejected on these grounds, considering the selective sample of studies included in the review.

There is one important limiting factor of functional imaging with PET, fMRI or Doppler, namely their weak temporal resolution. Consequently, the studies reviewed by Sommer and colleagues (Sommer *et al*., 2004) might have identified not only regions that are critical for language processing but also other areas that are activated while subjects solve the task, in particular when the control (subtraction) condition consists of 'passive' rest. This issue was discussed in detail in an earlier publication of the same group (Ramsey *et al*., 2001), in which they propose a combined analysis of several 'active' language conditions using so-called conjunction analysis to overcome the problem. In that study, the authors convincingly showed that the latter approach is more reliable for the study of language lateralization and yields a small amount of variance across subjects. Unfortunately, with the exception of one study (Sommer *et al*., 2003), the reports considered in the meta-analysis did not use this approach. On the contrary, six of the 14 selected studies contrasted activation during a language task with a 'passive' control condition (block design). Five of these six studies were among those that did not find sex differences.

The limitation in temporal resolution does not apply to brain mapping methods such as the recording of event-related potentials (ERPs) or magnetic fields (MEG). Consequently, these methods make it possible to functionally define and temporally restrict the analysis window to the task-relevant processing steps. In the study of language, the functionally relevant time interval would correspond to ~170–400 ms after stimulus onset, as many previous studies have reported the critical language-related ERP responses to occur in this window (for reviews see e.g. Khateb *et al*., 1999; Cohen *et al*., 2000; Kutas and Federmeier, 2000; van den Brink *et al*., 2001; Friederici and Kotz, 2003; Cohen and Dehaene, 2004). Sex differences in lateralization of language processing should consequently be most dominant (if not restricted) to this critical period of around 200 ms in length. Indeed, a recent MEG study by Walla and colleagues provides evidence for gender differences in word recognition in exactly this time window, i.e. between 200 and 350 ms (Walla *et al*., 2001). Beside differences in strengths of activation, topographical differences were found in this time period that were interpreted as reduced asymmetry in females compared with males.

The point we want to make is that brain imaging techniques that can be used to reveal functional neuronal activity in a precise, predefined time window may refine our understanding of functional brain asymmetries and should be considered before rejecting the hypothesis of sex differences in language representation. This will be further illustrated with a re-analysis of an ERP data set that has been published in part previously (Ortigue *et al*., 2004). In contrast to

Walla and colleagues, who provided indirect evidence on the lateralization of the neuronal activity since only surface maps were compared (Walla *et al*., 2001), here we apply a distributed inverse solution to determine the underlying electric sources of the recorded ERP surface maps.

While the precise spatial resolution of distributed inverse solutions is still debated, the ability to differentiate left and right hemispheric activation is not questioned (for a review see Michel *et al*., 2004). For the present purpose, we used these 3D current density estimations to calculate a measure for the difference between the amounts of activity in the two hemispheres (the lateralization index) as a function of time after stimulus onset.

Electrical brain activity was recorded simultaneously from 123 electrodes (Electrical Geodesics, USA; sampling rate 500 Hz; band-pass filtered at 0.01–200 Hz) in 26 healthy right-handed volunteers (13 women, mean age 24.8 ± 3.2 years; 13 men, mean age 26 ± 5.7 years) performing a bilateral lexical decision task. The task consisted of a go/no-go paradigm (go trials used bilateral word/non-word pairs, no-go trials used bilateral non-word/non-word pairs) with stimulus pairs presented for 13 ms only (interstimulus interval 1500–2000 ms; for details see Ortigue *et al*., 2004). This bilateral paradigm was selected as it has been shown to maximize hemispheric independence (Wey *et al*., 1993). Subjects were asked to respond as quickly as possible to a word by pressing a button according to perceived word location, i.e. with their left and right index finger for left- and right-sided words respectively. Individual ERPs to go trials from 0 to 500 ms after stimulus onset (only trials with correct responses were considered) were subjected to a distributed EEG source analysis procedure (LAURA; Grave de Peralta Menendez *et al*., 2004), resulting in a current density value for each of 4024 solution points regularly distributed in the grey matter of a realistic average head model (for details see Michel *et al*., 2004). The LAURA estimates of cerebral activity were then used to calculate for each subject separately an index of cerebral laterality for each moment in time (2 ms resolution). These laterality indices (LIs) were calculated for each time frame according to the following formula: LI = (left brain activity – right brain activity)/(left brain activity + right brain activity). Thus, positive values indicate left lateralization and negative values right lateralization of cerebral activity.

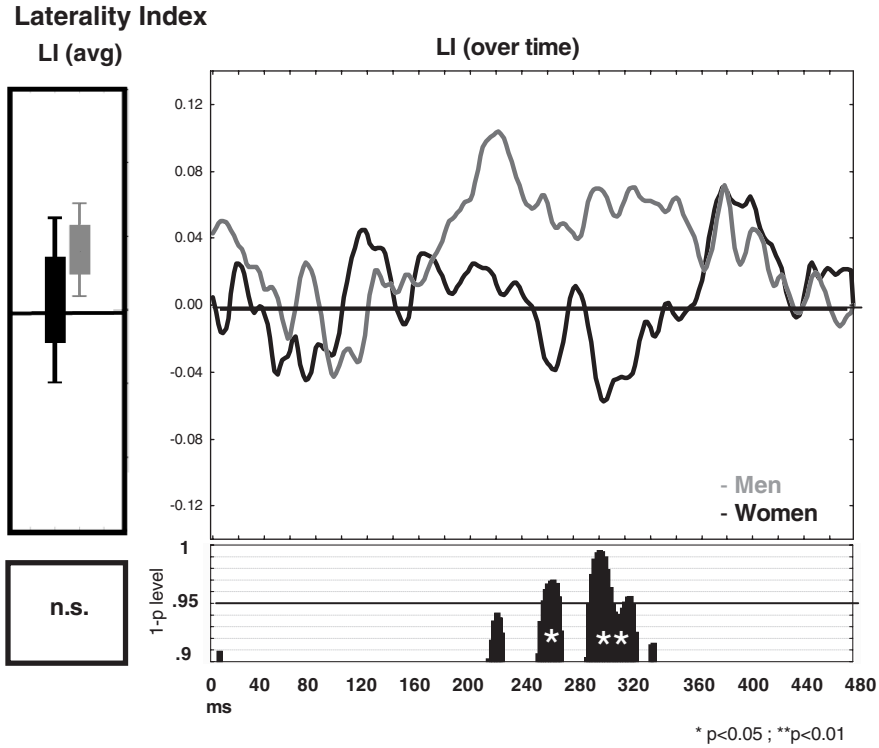

Fig. 1 Cerebral laterality indices (LIs) calculated from the distributed inverse solutions of each individual 123-channel evoked potential at each time point (2 ms resolution). The LI was calculated for each time frame according to the following formula: LI = (left brain activity – right brain activity)/(left brain activity + right brain activity). Thus, positive values indicate left lateralization and negative values right lateralization of cerebral activity. Mean of the LI over time are shown for men (grey) and for women (black). When data were averaged over all time samples (500 ms) to simulate a recording of low temporal resolution, LIs did not show any significant difference between genders (left panel). However, when the time course of the cerebral LI was taken into account, clear sex differences were observed between ~180 and 380 ms after stimulus onset (right panels). Over this period, men showed clearly left-lateralized cerebral activation, while women exhibited less consistent asymmetry. Only at later time points (380–450 ms) was cerebral activity of both genders lateralized to the left hemisphere. The earlier sex differences in LIs were significant at various intervals after stimulus onset, as revealed by pointwise *t*-tests for each time frame (the statistical results are illustrated in the lower panel).

The results suggest that when the time course of the cerebral LI is taken into account, clear sex differences are observed between ~180 and 380 ms after stimulus onset (Fig. 1, right panels). Over this period, men showed clearly left-lateralized cerebral activation (positive deflection in LI, maximum LI = +0.1), while women exhibited less consistent asymmetry (Fig. 1, upper right panels). The early sex difference in LI was significant at various intervals after stimulus onset, as revealed by *t*-tests for each time frame (Fig. 1, lower panel illustrates the statistical results). These time periods of significant sex differences match those found in the MEG study by Walla and colleagues (Walla *et al*., 2001) and correspond to the components generally found to be relevant for language processing, i.e. between 170 and 400 ms (see above). Hence, the fact that our data indicate significant sex differences in this time window strongly suggests that language-related processes differ between men and women while other perceptual and motor components involved in the task do not differ. Importantly, sex differences became non-significant when evoked activity was integrated over a longer time period (i.e. 500 ms or all time samples) to simulate a recording of low temporal resolution [Fig. 1, left panel, *t*-test (–1.04); $P = 0.3$]. Thus, if integrated over all samples, our recordings would indicate that cerebral activity associated with the processing of words does not lateralize differently between genders. This would favour the view of similar language lateralization in women and men, as advocated by Sommer and colleagues (Sommer *et al*., 2004).

In conclusion, we argue that sex differences in language processing might be hard to detect with conventional functional imaging studies because they are restricted to the time period when language processing actually takes place. This period lasts ~200 ms and might thus be too short to become evident using imaging techniques with a low time resolution. ERP and MEG combined with source imaging procedures can provide another dimension to the understanding of functional brain organization in men and women. They allow the unraveling of the electrical brain activity within the large-scale neuronal networks involved in cognition in the millisecond range.

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